IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

McKENZIE et al.

Serial No.: 09/163,089

Filed: September 29, 1998

Atty. File No.: 4102-1

For: "COMPOSITIONS FOR IMMUNOTHERAPY AND USES THEREOF"

Group Art Unit: 1631

Examiner: Siu, S.

DECLARATION OF
DR. GEOFFREY A PIETERSZ
(Under 37 CFR 1.132)

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO COMMISSIONER OF PATENTS, WASHINGTON, D.C., 20231 ON MAY 11, 2001.

SHERIDAN ROSS P.C.

BY: Constance Rosnell

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Geoffrey A Pietersz, declare as follows:

1. I am a co-inventor of the above-referenced patent application and am familiar with the application. I am a skilled artisan in the field of immunology.

2. This Declaration is being submitted in conjunction with an Amendment and Response to the final Office Action having a mailing date of February 13, 2001.

3. The following discussion is provided in traverse of the Examiner's rejection of Claims 13-16 and Claims 1, 3-21, 23-34, 36-45 and 47-51 under 35 U.S.C. § 112, first paragraph.

4. With regard to the rejection of Claims 13-16, the Examiner asserts that the specification does not show that peptide fragments of 5 amino acids would be immunogenic and states that the prior art shows that peptides must be 10-20 amino acids in length in order to be presented by MHC Class I molecules. The Examiner supports this position by citing "Cellular and Molecular Biology", Abbas et al. (MJ Wonsiewicz, ed.), WB Saunders Company, Philadelphia, USA, 1991.

I respectfully submit that the Examiner is incorrect in the assumption that peptide fragments of 5 amino acids would not be immunogenic and that peptides must be 10-20 amino acids in length to be presented by MHC Class I.

a. First, as illustrated in attached Figure 1, unpublished experiments performed in my laboratory (described in Document 1) show that cytotoxic T lymphocytes (CTLs) are capable of recognizing target RMA-S cells that present MUC1 peptides between 5 and 9 amino acids in length.

b. Second, contrary to the Examiner's position that peptides must be 10-20 amino acids in length to be presented by MHC Class I, the Examiner is respectfully referred to the following 3 publications, which show that a 5-mer peptide is presented by MHC Class I:

1. Eisen et al., 1996, *Adv. Protein Chem.* 49:1-56;
2. Gillanders et al., 1997, *Int. Immunol.* 9:81-89; and,
3. Reddehase et al., 1989, *Nature* 337:651-653.

c. Third, the Examiner is respectfully directed to the attached page 187 of "Immunology: A Short Course", Benjamini et al., Wiley-Liss, New York, USA, 1996, wherein it is stated that MHC Class I molecules "preferentially bind peptides of 8 or 9 amino acids."

d. Fourth, enclosed is a publication by the present inventors which shows that 8-mer peptide mimic of MUC1 is capable of inducing CTL responses (Apostolopoulous et al., 1998, *Nature Biotech.* 16:276-280.

c. Fifth, it is believed that the composition described by the present invention is particularly effective and immunogenic by virtue of the presence of aldehyde groups in the antigen-carbohydrate polymer conjugate (see page 29, lines 8-13 of the specification). The claims recite a conjugate having aldehydes, and therefore, the claimed composition is immunogenic by virtue of the presence of the aldehydes.

In summary, it is submitted that the prior art does not predict the failure of immunogenicity of fragments that are 5 amino acids in length, nor does the prior art at the time of the invention teach that MHC Class I peptides must be 10-20 amino acids in length. I and the co-inventors have demonstrated that peptides smaller than 10 amino acids, including 5-mer peptides, as well as conjugates meeting the limitations of the claims, are in fact immunogenic.

5. With regard to the Examiner's position that the specification is not enabling for conjugates in which the carbohydrate polymer contains only one mannose, I submit that a skilled artisan, using the guidance in the instant specification, would be able to produce a carbohydrate polymer containing mannose and that such a polymer would be immunogenic.

More specifically, the skilled artisan would be able to produce a carbohydrate polymer containing mannose by first synthesizing a backbone chain wherein the carbohydrate monomers may include mannose and any one or a mixture of carbohydrate monomers such as those disclosed on page 28, lines 1-10 of the present specification. This carbohydrate polymer could be activated and conjugated to an antigen as disclosed at pages 28, line 16 to page 32, line 9.

It is further submitted that conjugates in which the carbohydrate polymer comprises at least one mannose is capable of being immunogenic, because even one mannose can bind to a mannose receptor present on, for example, macrophages and dendritic cells, thereby stimulating an immune response as demonstrated in the present specification. In support of this position, enclosed is a publication by the present inventors (Apostolopoulous et al., 2000, *Eur. J. Immunol.* 30:1714-1723). As described in paragraph 2.2.1 on page 1715, binding of oxidized or reduced mannose-FITC (M-FITC) to a macrophage cell line was inhibited by D-mannose. Furthermore, as described in the paragraph bridging pages 1715-1716, and as shown in Fig. 2, a conjugate of mannan-MUC1 (shown to be immunogenic by the present specification and Document 3) can inhibit the binding of mannose to soluble mannose receptors. These results indicate that, if mannose (even one) is present in a conjugate of antigen-carbohydrate polymer, such a conjugate can bind to a mannose receptor on cells (e.g., macrophages or dendritic cells), thereby allowing the conjugate to induce an immunogenic response as shown in the present specification.

In summary, the mannose component of the claimed conjugate binds to mannose receptors on antigen presenting cells, thereby enabling the conjugate, which is immunogenic by virtue of the antigen and aldehyde groups, to induce an immune response. Even one mannose in the carbohydrate polymer would bind to a mannose receptor on a cell, thereby enabling the production and use of the presently claimed compositions.

6. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

Date: 11/5/01 By: G. A. Pietersz

Geoffrey A Pietersz